Bupivacaine: A Review

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ABSTRACT

A review of current significant literature concerning bupivacaine hydrochloride (Marcaine) is presented with particular emphasis on clinical use in oral surgery. The major advantages compared with other presently used local anesthetics are an increased duration of action and a favorable potency to toxicity ratio.

Bupivacaine HCL (1-butyl-2', 6' pipecoloxylidide hydrochloride)* is a long acting amide local anesthetic (Fig. 1). First synthesized in 1957 by Ekenstam at A.B. Bafors Laboratories in Mölndel, Sweden, this drug has undergone trials and varying degrees of acceptance in virtually every area of local anesthetic practice.[1]

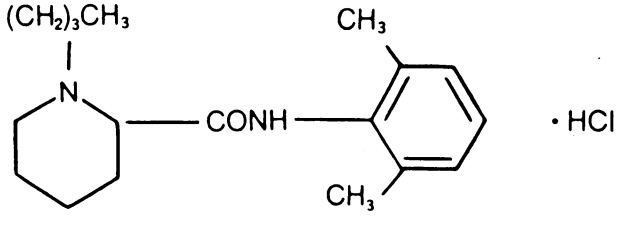

Figure 1
Chemical Structure of Bupivacaine

Mechanism of Action

The mechanism of action of bupivacaine is presumed to be the same as for other local anesthetics. Current local anesthetic theory holds that these compounds obstruct the inward flow of sodium ions through the nerve membrane, thus preventing the generation of an action potential.[2] Competitive binding to calcium sites is postulated to occur in the external lipid layer of the nerve membrane with resultant secondary interference of mobile phosphate groups. Passage of sodium ions is blocked by preventing molecular membrane reconfiguration from the resting (sodium impermeable) to the active (sodium permeable) state.

The increased duration of action of bupivacaine is ascribed to its affinity for nerve tissue.[3]

Clinical Use

Bupivacaine is utilized for intraoperative local anesthesia, post operative analgesia and in the treatment of chronic pain.

Bupivacaine is widely used in obstetrics. In lumbar epidural anesthesia the drug appears innocuous to mother and fetus.[4,5] The acceptable therapeutic index is largely due to the small amount of drug needed per unit time. The indications for bupivacaine in obstetrical analgesia are enhanced by the insignificant motor blockade in concentrations less than 0.5%.[6,7]

Caudal blocks with bupivacaine for vaginal delivery are more efficacious due to the increased duration of analgesia,[8,9,10] however fetal deaths have been reported secondary to paracervical block.[11] This latter method of administration is contraindicated unless epidural block is incomplete or unavailable at a given institution.

Excellent sensory anesthesia is reported with 0.5% bupivacaine epidural blocks for thoracic and abdominal surgery.[12,13] The increased duration of action postpones the patients initial request for post operative analgesics.[13] Continuous thoracic epidural infusion of 1.0% bupivacaine does not provide analgesia of greater duration than lesser concentrations of bupivacaine.[14] Furthermore, tachyphalaxis, extensive segmental spread, urinary retention, high plasma drug concentrations, and inadequate operative anesthesia may occur.

Intraoperative anesthesia by intercostal injection of bupivacaine is effective,[15,16,17] with a duration of four[15] to five[16] hours.

Bupivacaine combined with 2-chlorprocaine for brachial plexus blocks provides rapid onset and an increased duration of anesthesia over 2-chlorprocaine alone.[18,19] No toxic reactions and a quiescent post operative period are reported.[18,19]

In ulnar nerve block, bupivacaine 0.25% or 0.5% provides excellent sensory and sympathetic anesthesia, but motor paralysis is not complete. Initial onset for sensory fibers in within eight minutes.[20]

For intravenous regional anesthesia, bupivacaine provides rapid onset (3-5 minutes), good muscle relaxation, and fewer toxic reactions relative to lidocaine.[21]

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Bupivacaine has also been used in non-surgical procedures. Epidural administration has provided total resolution of non-malignant chronic pain.[23] In a limited study,[24] intra-gasserian ganglionic injection of bupivacaine moderated exacerbations of trigeminal neuralgia.

Clinical Effectiveness

Effectiveness of bupivacaine is evaluated by toxicity to potency ratio, latency of onset, degree of sympathetic, sensory, and motor block, duration of analgesia, and regression time. Statistical data and clinical results are inseparably related to the vascularity of the area of injection and the concentration and quantity of the agents used.[25,26]

Bupivacaine 0.5% initially appeared approximately equitoxic-equipotent to 0.5% tetracaine,[26,27] 2.0% lidocaine,[5,26,28,29] 3.0% mepivacaine,[26,27,28] and 1.0% etidocaine.[6,7,16,29,30,31,32] More recent literature reveals a toxicity to potency ratio even more favorable than previously stated.[33] The onset of action of bupivacaine (2-10 minutes, variable with source and nature of injection) is similar to tetracaine[26] and mepivacaine[26] but is somewhat slower than lidocaine,[26,34,35] prilocaine,[26] and etidocaine.[7,20,36]

Sympathetic fibers are more easily blocked than sensory or motor fibers.[26] Sympathetic blocks may manifest themselves in clinical phenomena as Horner's syndrome[38] or hypotension.[37] Bupivacaine blocks sympathetic fibers more effectively than etidocaine.[20]

Löfström[26] contends that in equitosic-equipotent doses, bupivacaine provides as complete and profound a sensory block as tetracaine, lidocaine, prilocaine, and mepivacaine.

Bupivacaine, prilocaine, and mepivacaine all provide complete motor blocks.[26] Both tetracaine[26] and etidocaine[6,7,20,31,32,36,39,40] produce a more profound motor block than bupivacaine.

Bupivacaine, tetracaine and etidocaine have much longer durations of action than other local anesthestics. In equitoxic-equipotent doses, bupivacaine shows longer and more profound sensory blocks than either tetracaine[26] or etidocaine.[6,7,31,32,36,39] Peripheral nerve blocks[26,35] of eight to twelve hours and intercostal blocks[26] or 14 hours are reported. Vasoconstrictors with bupivacaine do not increase the duration of anesthetic action.[6,26,40,41]

Regression time (the time from reappearance of pain perception until complete recovery of pain sensation) is longer with bupivacaine than with other agents.[26,35]

Tachyphylaxis appears less likely with this agent than with other local anesthetics because fewer injections are usually made.[5,26]

Bioavailability

The biologic fate of bupivacaine is dependent on absorption, distribution, and elimination.[42]

Absorption and distribution are influenced by the vascularity of the injection site, mode of injection, and the degree of drug ionization.[42]

Highly vascularized sites contribute to an increased drug plasma concentration.[25,42]

Intravenous administration provides a peak plasma concentration shortly after injection.[42] At this point, the drug's half life is 45 minutes which corresponds to tissue redistribution. Four hours after IV administration, T½ becomes 2½ hours due to elimination. IV drip infusion results in a slower increase in plasma concentration and a tendency to plateau which is indicative of equilibrium.[42] Injection for nerve block results in maximum plasma levels in 15 to 30 minutes.[43]

Local anesthetics are weak bases and diffuse through membranes as a lipid soluble unionized moiety.[42] Therefore, physiologic alterations such as acidosis, which change bupivacaine to its ionized form, will inhibit membrane transport, delay onset, decrease effectiveness, decrease plasma concentrations, decrease toxicity, and decrease elimination via decreased delivery to liver and kidneys.[42]

As with other amide local anesthetics[44] bupivacaine is mainly metabolized in the liver by N-dealkylation and glucuronide conjugation of the hydroxylated parent compound.[45] Time for metabolism of bupivacaine is equal to lidocaine and etidocaine.[46] Elimination is mainly via urinary excretion; however, some excretion of metabolites via the lungs and bile undoubtedly occurs.[47] Very little unchanged drug is recovered in the urine.[45,48]

Bupivacaine is highly bound to non-albumin plasma proteins.[42] This binding is more extensive than either lidocaine or mepivacaine,[42] but equal to etidocaine.[49] Subsequent distribution of bupivacaine and etidocaine is greater than lidocaine and mepivacaine.[46] This increased protein binding results in a decreased tissue to blood coefficient. Therefore, the drug is presented to the liver quickly, but hepatic uptake is slow.[42] Protein binding contributes to a decreased fetal to maternal drug concentration ratio, which increases the safety of this agent in obstetrics.[10] Epinephrine decreased fetal bupivacaine levels further in one study.[50]

The bound fraction of bupivacaine is pharmacologically inactive; it is the unbound fraction which is responsible for toxic reactions.[42] Demerol, diphenylhydantoin, quinidine, and desipramine all readily displace bupivacaine from protein binding sites.[51] However, the apparent increased potential for bupivacaine toxicity is not realized since erythrocyte binding sites readily absorb the displaced drug.[51]

Toxicity

Systemic local toxicity manifests itself in slurred speech, nystagmus, twitching, disorientation, circumoral numbness, lightheadedness, paresthesias, drowsiness, and convulsions.[38,52] These CNS effects usually manifest themselves before ventilatory or circulatory compromise.[53,54]

Toxicity increases with increasing rate of epidural infusion.[29,52] Intermittant epidural block increases effectiveness and decreases toxicity compared with continuous infusiom.[38] Bupivacaine appears slightly more

toxic than etidocaine which is slightly more toxic than lidocaine. Despite the differences in absolute toxicities, the potency to toxicity ratios are approximately equal.[29]

Drowsiness after bupivacaine injection appears with arterial plasma concentrations greater than 1.5 ug/ml, peripheral paresthesias at 2.0 ug/ml and convulsions occur near 4.0 ug/ml.[48] Convulsions have been reported after bupivacaine injection in labor when the venous drug concentration was 2.3 ug/ml,[54] as might be expected since peripheral venous bupivacaine concentration is less than concomitant arterial plasma concentration.[29,33] Psychomotor impairment in automobile driving appears after 1.3 ug/kg of bupivacaine is administered instramuscularly.[55]

The amygdala is believed to be the primary locus of activity in local anesthetic seizures.[29,56] Scott[52] however, found no localized EEG changes during clinical CNS reactions to bupivacaine. Seizure threshold experiments in monkeys failed to localize aberrent EEG activity.[29] Short acting barbiturates and benzodiazepine derivatives are the anticonvulsants of choice for treatment of these seizures.[29,53,56]

Hypotension due to epidural blocks occurs occasionally[57,58] and is secondary to sympathetic blockade[38] or maternal caval occlusion.[58] Fetal bradycardia is a rare complication[57,58] but Apgar scores for infants delivered with bupivacaine epidural anesthesia are not affected.[48]

Previously, maximum doses of bupivacaine have been stated as 150-225 mg. every three hours and 400 mg. every 24 hours. These now appear conservative,[54] although insufficient data exists to accurately define maximum toxic doses.

Neuro toxicity with 0.5% bupivacaine has been suspected when blocks in excess of 60 hours have been achieved.[59] Another indication of local toxicity is the reduced vasodilatory response to ischemia in the presence of bupivacaine.[22]

Use in Oral Surgery

Attempts to use the increased duration of action of bupivacaine to modify post operative oral surgical pain have been made.[28,34,35,60,61] Rapid onset, profound surgical anesthesia, lack of toxic reactions, and increased duration of action have been realized. With the exception of Hellden and Associates,[28] studies have shown a significant delay in initial request for post operative analgesia.[34,35,60,61] Laskin and Associates,[35] describe a protracted period of post operative analgesia persisting after normal sensation has returned. Local anesthetic agents in the perioral area are subject to a decreased duration of action secondary to the vascularity of the area.[25,28] Nevertheless, obtundation of post operative oral surgical pain for up to twelve hours is reported.[35]

Feldman and Norderam's[60] original oral surgical statistics indicated no difference in duration of action between 0.25% and 0.5% bupivacaine. More recent oral surgical studies indicate that onset, duration, and degree of surgical anesthesia are enhanced by increasing drug concentrations.[28,34,35,61]

Studies comparing bupivacaine with and without vasoconstrictors demonstrate no significant differences in duration between these groups.[6,26,39,40] Prolongation of bupivacaine block in oral surgery may be achieved by combination with low molecular weight dextran -40. In one study, the mean duration of post operative analgesia in the bupivacaine-dextran group was 36 hours compared to 12 hours for the bupivacaine-saline control.[62] The mechanism suggested is the formation of a dextran-bupivacaine complex which is absorbed much more slowly than bupivacaine alone.

Discussion

Bupivacaine is a long acting local anesthetic that is becoming extensively used in clinical practice. The potency to toxicity ratio (anesthetic index) is favorable when compared to other currently used local anesthetics.

In oral surgery, this drug provides excellent surgical anesthesia and extended post operative analgesia. Bupivacaine is ideally suited for use in providing relief of severe dental pain when definitive treatment is to be postponed. Additionally, periodontal surgery as well as prolong dental restorative procedures would benefit from bupivacaine anesthesia.

The possibilities for self-mutilation must always be considered when contemplating the use of a long-acting perioral local anesthetic.

The excellent results with bupivacaine underscore its clinical efficacy and motivate continued use and evaluation in oral surgery.

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